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L1: Entry 89 of 104

File: USPT

Jun 18, 1996

DOCUMENT-IDENTIFIER: US 5527528 A
TITLE: Solid-tumor treatment method

Drawing Description Paragraph Right (1):

FIGS. 1A-1C are representations of antibody-liposome compositions, in which (a) an antibody molecule is directly attached to a liposome surface (FIG. 1A), (b) an antibody molecule is attached to a liposome surface by a polyethylene glycol (PEG) chain with a functionalized reactive end group (FIG. 1B), and (c) an antibody molecule is bound by biotin/avidin coupling to a liposome having surface-bound biotin moieties (FIG. 1C);

Detailed Description Paragraph Right (13):

In one particular embodiment, illustrated in FIG. 1B, the antibody molecule in the composition is attached to the liposome outer surface by a polymer spacer chain. The figure shows a liposome bilayer portion 24 with a layer 26 of PEG chains, as above. The antibody, such as antibody 28, is attached to the liposome outer surface by a spacer chain, such as chain 30. The spacer chain is preferably a hydrophilic chain, such as a 100-5,000 dalton PEG chain, which is itself coupled to the polar head group of a lipid, such as lipid 32, in the outer layer 34 of the liposome bilayer. The spacer chain contains a reactive functionalized group 36 at its free end for coupling antibody.

Detailed Description Paragraph Right (16):

The figure shows a liposome bilayer portion 40 with a layer 42 of PEG chains, as above. The liposome outer surface contains a number of lipid polar head groups, such as lipid polar head group 44, which have been derivatized by biotin. To a biotin moiety on the liposome surface, such as biotin moiety 46, is bound an avidin molecule, such as avidin molecule 48. Each avidin molecule contains four high-affinity biotin binding sites, such as biotin binding site 50. To one or more of these sites is attached the liposome bound biotin as previously indicated. To one or more of the free-remaining sites can be bound a biotinylated antibody, such as biotinylated polypeptide 52, which is derivatized by a biotin molecule, such as biotin molecule 54.

Detailed Description Paragraph Right (49):

Liposome compositions are typically prepared with lipid components present in a molar ratio of about 30-75 percent vesicle-forming lipids, 25-40 percent cholesterol, 1-20 percent polymer-derivatized lipid, and 0.01-10 mole percent of the lipid derivative employed for antibody coupling. One exemplary liposome formulation includes hydrogenated soy phosphatidylethanolamine (HSPE), cholesterol (CH), DSPE-PEG at a molar ratio of 2:1:0.1. The composition also includes 0.05 mole percent phosphatidylethanolamine derivatized with biotin (biotin-PE). Another exemplary liposome formulation includes hydrogenated soy phosphatidylethanolamine (HSPE), cholesterol (CH), and DSPE-PEG at a molar ratio of 2:1:0.1. The composition also includes 1 mole percent DSPE-PEG derivatized with hydrazide (DSPE-PEG HZ).

Detailed Description Paragraph Right (55):

Alternatively, an antibody-lipid derivative may be first formed and then incorporated into a liposome. As an example, an antibody is coupled to the maleimide group of a free DSPE-PEG molecule. The antibody-coupled DSPE-PEG molecule is then employed to form vesicles.

Detailed Description Paragraph Right (57):

Alternatively, the polymer end-functionalized group is a hydrazide group. For antibody coupling to the liposome surface, antibody hydroxyl groups are oxidized to aldehydes by mild periodate oxidation. The periodate-treated protein is added to liposomes containing DSPE-PEG hydrazide and incubated overnight. Unbound antibodies are then separated from the antibody-liposomes by gel filtration. The procedure is described in Example 2.

Detailed Description Paragraph Right (58):

An exemplary method for attaching antibodies noncovalently to liposomes is illustrated in FIGS. 5A and 5B. FIG. 5A shows the preparation of a biotinylated monoclonal IgG antibody to generate compound X. FIG. 5B shows coupling of biotinylated antibody to the liposome surface by first binding avidin, represented in FIG. 5B as a rectangle divided into 4 parts, to the liposomes, then incubating the avidin-coated liposomes with the biotinylated antibody. Experiments conducted in support of the present invention indicate that antibodies are efficiently attached to PEG-coated liposomes by this method. Details are given in Example 3.

Detailed Description Paragraph Right (61):

Experiments were performed to investigate the half-life in the bloodstream and the tissue biodistribution of the antibody-liposome composition. For these experiments liposomes containing PEG end-functionalized with a hydrazide group covalently linked to sheep IgG were prepared as described in Example 2.

Detailed Description Paragraph Right (62):

Other experiments to determine the blood circulation times of antibody-liposomes were performed using liposomes containing surface-bound avidin and biotinylated antibodies. Liposomes with surface-bound antibodies possessed long circulation times in the bloodstream similar to that of liposomes containing PEG derivatized lipids but lacking the surface-bound antibodies. Twenty-four hours post-injection 34.7+-.6.7% of mAb liposomes were in the blood. This level is comparable to that of liposomes containing PEG, but lacking the antibody (37.5+-.9.7% at 24 hours).

Detailed Description Paragraph Right (63):

As shown in Table 1 the tissue biodistribution of liposomes containing antibody covalently attached to the end of a PEG chain by a hydrazide group is very similar to those of liposomes containing nonfunctionalized PEG chains. Liposome biodistribution was determined for the blood, liver, spleen, lung, heart and carcass.

Detailed Description Paragraph Right (71):

The results obtained indicate that liposomes containing entrapped doxorubicin, lipids derivatized with PEG, such as PEG-DSPE, and containing an antibody on the liposomes' outer surface (mAb-liposomal DOX) are valuable for increasing the therapeutic effectiveness of doxorubicin administration to a site in a subject. The method of the present invention is likely applicable to the targeting of other therapeutic compounds to tumor sites, or other target sites.

Detailed Description Paragraph Right (79):

These multivalent species serve to chase nonspecifically-bound biotinylated antibodies from sites in the bloodstream. After the chase, liposomes containing the therapeutic compound in liposome-entrapped form, the surface-bound anti-ligand molecules, such as avidin, and the PEG layer on the liposome surface are administered. Performing the chase with the multivalent species will prevent binding of liposomes containing liposome entrapped-drug at non-specific sites and will maximize the specificity of therapeutic compound targeting in vivo.

Detailed Description Paragraph Right (107):

The biodistribution of liposomes containing surface-bound antibodies was compared to that of liposomes lacking surface-bound antibodies. The antibody-liposomes were composed of HSPC:CH:PEG hydrazide, at 2:1:0.1 molar and sheep IgG covalently linked to PEG chain. Liposomes lacking surface-bound antigens were liposomes composed of HSPC:CH:PEG at a 2:1:0.1 molar and liposomes composed of HSPC:CH:PEG hydrazide. The average diameter of the liposomes was between 110 and 120 nanometers. For biodistribution studies the liposomes contained .sup.125 I-tyraminylinulin in liposome-entrapped form.

Detailed Description Paragraph Right (108):

The antibody-liposomes were prepared as described. A 10 mg/ml solution of IgG was prepared in 100 mM sodium acetate, 70 mMNaCl pH 5.5. For 1 ml of the protein solution, 55 microliters of 0.2M sodium periodate was added. Oxidation proceeded for 1 hour at room temperature. The periodate-treated protein was added to liposomes containing DSPE-PEG hydrazide and incubated overnight at 4.degree. C. Liposomes were separated from free protein by chromatography on Sepharose CL-4B in TES-buffered saline, pH 7.4.

Detailed Description Paragraph Right (111):

As shown in Table 1 the biodistribution of liposomes containing antibody covalently attached to the end of a PEG chain by a hydrazide group are very similar to those of liposomes containing nonfunctionalized PEG chains. Liposome biodistribution was determined for the blood, liver, spleen, lung, heart and carcass.

WEST**End of Result Set**

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L1: Entry 104 of 104

File: DWPI

Oct 13, 1994

DERWENT-ACC-NO: 1994-332780

DERWENT-WEEK: 199927

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TITLE: Liposome compsn. for tumour treatment - comprising liposome(s) contg. an anti-tumour cpds. with a polyethylene glycol coating and attached antibodies

Basic Abstract Text:

A liposome compsn. for use in tumour treatment comprises (a) liposomes having sizes predominantly in the range 0.05 to 0.3 μ m and contg. an anti-tumour cpd. in liposome-entrapped form, (b) a surface coating of polyethylene glycol (PEG) chains on the liposomes at a surface concn. sufficient to extend the blood circulation time of the liposomes several-fold, over that of liposomes in the absence of such coating; and (c) antibodies or antibody fragments effective to bind specifically to tumour-associated antigens, where the PEG chains contain, in a portion of them, functionalised reactive gps. at the chain ends to which the antibodies or antibody fragments are covalently attached.

Basic Abstract Text (1):

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WEST Search History

DATE: Monday, March 25, 2002

<u>Set Name</u> side by side	<u>Query</u>	<u>Hit Count</u>	<u>Set Name</u> result set
<i>DB=USPT,JPAB,EPAB,DWPI,TDBD; PLUR=YES; OP=OR</i>			
L1	liposome\$ same antibod\$ same PEG	104	L1

END OF SEARCH HISTORY

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L1: Entry 55 of 104

File: USPT

Nov 30, 1999

DOCUMENT-IDENTIFIER: US 5994511 A

TITLE: Anti-IgE antibodies and methods of improving polypeptides

Detailed Description Paragraph Right (186):

Particularly useful liposomes can be generated by the reverse phase evaporation method with a lipid composition comprising phosphatidylcholine, cholesterol and PEG-derivatized phosphatidylethanolamine (PEG-PE). Liposomes are extruded through filters of defined pore size to yield liposomes with the desired diameter. Fab' fragments of the antibody of the present invention can be conjugated to the liposomes as described in Martin et al., J. Biol. Chem. 257: 286-288 (1982) via a disulfide interchange reaction. A chemotherapeutic agent (such as Doxorubicin) is optionally contained within the liposome. See Gabizon et al., J. National Cancer Inst. 81(19): 1484 (1989).

WEST

Generate Collection

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L1: Entry 65 of 104

File: USPT

Oct 13, 1998

DOCUMENT-IDENTIFIER: US 5820873 A

TITLE: Polyethylene glycol modified ceramide lipids and liposome uses thereof

Detailed Description Paragraph Right (1):

The PEG-modified ceramide lipids of Formula I enhance the properties of liposomes by increasing the circulation longevity or lifetime of the liposome; preventing aggregation of the liposomes during covalent protein coupling, such as for targeting; preventing aggregation of liposomes incorporating targeting moieties or drugs, such as antibodies, and DNA; promoting drug retention within the liposome; and/or increasing bilayer or other stability of the liposome when low pH is required for encapsulation of the bioactive agents. These PEG-Ceramide lipids also reduce leakage due to hydrolysis of the fatty acyl chains of the liposome bilayer and are more stable than other lipid forms.

Detailed Description Paragraph Right (49):

Liposomes with targeting molecules can be used to stimulate or suppress a cell. For example, liposomes incorporating a particular antigen can be employed to stimulate the B cell population displaying surface antibody that specifically binds that antigen. Similarly, PEG-stabilized liposomes incorporating growth factors or lymphokines on the liposome surface can be directed to stimulate cells expressing the appropriate receptors for these factors. Such an approach can be used for example, in stimulating bone marrow cells to proliferate as part of the treatment of cancer patients following radiation or chemotherapy which destroys stem cells and actively dividing cells.

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Generate Collection

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L1: Entry 68 of 104

File: USPT

Jun 30, 1998

DOCUMENT-IDENTIFIER: US 5773027 A

TITLE: Liposomes encapsulating antiviral drugs

Detailed Description Paragraph Right (2):

The liposomes of the present invention include sterically stabilized liposomes, defined herein as, liposomes composed of the lipid components mentioned above and which are modified by the incorporation of polymers, such as poloxamers and poloxamines, or of amphipathic lipids derivatized with a polymer such as DSPE-PEG or dioleoylphosphatidylethanolamine-PEG (DOPE-PEG). Details for the synthesis of DSPE-PEG are provided in Example 1. The liposomes of the present invention also include immunoliposomes, defined herein as, liposomes or sterically stabilized liposomes composed of the lipid components mentioned above and which are modified by the coupling of antibody molecules which enhance the targeting of specific cells.

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L1: Entry 74 of 104

File: USPT

Nov 11, 1997

DOCUMENT-IDENTIFIER: US 5686101 A

TITLE: Phospholipid derivative and liposome containing it

Detailed Description Paragraph Type 0 (8):Bonding of an antibody to the M-PEG-PE-containing liposome